UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE NUVARING® PRODUCTS LIABILITY LITIGATION	)	Case No. 4:08-MD-1964 RWS
	)	ALL CASES

MEMORANDUM AND ORDER

Defendants ("Organon") have moved to exclude all testimony during the course of this multi-district litigation ("MDL") related to "bursts" or "high variability" in NuvaRing's estrogen delivery. Organon asks me to find, as a matter of law, that none of Plaintiffs' experts is qualified and that any opinion on this subject from any expert would be so unreliable and so irrelevant that it should be excluded from being tested by any cross-examination at trial, being weighed by any jury, or even limited in any respect by any trial judge. After reading the voluminous briefs and exhibits filed by both sides on this issue, I am not persuaded that all testimony on bursts and estrogen variability should be excluded. Because I find that Plaintiffs have proffered experts who are qualified and who present relevant and reliable opinions, I will deny Organon's motion.

I. BACKGROUND

This MDL relates to the manufacture, marketing, and sale of the prescription pharmaceutical known as NuvaRing. NuvaRing, which is manufactured, marketed, and sold by Organon, is a member of a class of prescription drugs known as combined hormonal contraceptives ("CHCs"). Unlike oral CHCs, NuvaRing takes the form of a flexible ring which releases hormones over the course of treatment. The ring is vaginally inserted by women for birth control. Each month, the ring is removed and a new ring is inserted.

CHCs contain an estrogen, typically ethinyl estradiol ("EE"), and a progestin. The "generation" of CHC depends upon the type of progestin. Each "generation" of CHC typically

uses the following progestins: first-generation contains norethynodrel; second-generation contains levonorgestrel; and third-generation CHCs contain desogestrel, gestodene, or norgestimate. NuvaRing uses the active metabolite of desogestrel, etonogestrel, and is therefore considered a third-generation progestin.

First-generation CHCs use high levels of EE and are associated with high incidence rates venous thromboembolism ("VTE"), including deep vein thrombosis and pulmonary embolism.[1] Second-generation CHCs use a reduced amount of EE and are associated with less risk for VTE. It is generally accepted that risk of thrombosis is correlated with estrogen dose.

Third-generation CHCs use lower amounts of estrogen than prior generations; however, some studies have found an increased risk for VTE with some third-generation CHCs as compared to second-generation CHCs. Plaintiffs claim that the third-generation progestin used in NuvaRing, etonogestrel, has been linked to undisclosed higher risk for VTE, including both deep vein thrombosis and pulmonary embolism. Plaintiffs have asserted the following claims: strict products liability for defective manufacturing, defective design, failure to test, and inadequate warnings; breach of express / implied warranties; and negligence.

I have already ruled that Plaintiffs may adduce expert testimony that NuvaRing use presents an increased risk for VTE when compared with second-generation use.[2] Plaintiffs' experts opine that this increased risk results from the reduced ability of etonogestrel to counterbalance the prothrombotic (blood-clotting) effects of the estrogen component.

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[1] Venous thromboembolism is a blood clot that forms within a vein. Deep vein thrombosis is a blood clot that forms in a vein not externally visible, typically in the veins of the lower extremities. A pulmonary embolism forms when part or all of a blood clot breaks free and lodges in one of the lungs. These conditions have varying severity and can be life threatening.

[2] See Order dated March 4, 2013, denying Organon's motion to exclude testimony that hormone "counterbalance" or surrogate markers can assess the risk of VTE in hormonal contraceptives (Doc. 1307).

I have also already ruled that Plaintiffs' expert, Dr. Shelly Tischkau, is qualified to testify as an expert on pharmacokinetics and may testify on topics related to the variability of NuvaRing's estrogen delivery system.[3] I have further held that Plaintiffs' expert Dr. Suzanne Parisian is qualified to testify as an expert on topics related to NuvaRing's label and its pharmacological data.[4]

II. LEGAL STANDARD

Federal Rule of Evidence 702 and Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), govern the admissibility of expert testimony. The Daubert standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. See Polski v. Quigley Corp., 538 F.3d 836, 838 (8th Cir. 2008). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

"[I]t is the responsibility of the trial judge to determine whether a particular expert has sufficient specialized knowledge to assist jurors in deciding the specific issues in the case." Wheeling Pittsburgh Steel Corp. v. Beelman River Terminals, Inc., 254 F.3d 706, 715 (8th Cir. 2001). "Once initial expert qualifications and usefulness to the jury are established, however, a district court must continue to perform its gatekeeping role by ensuring that the actual testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable . . . ." Id.

[3] See Order dated March 4, 2013, denying Organon's motion to exclude testimony of Plaintiffs' expert Shelly Ann Tischkau, Ph.D. (Doc. 1297).

[4] See Order dated March 4, 2013, denying Organon's motion to exclude testimony of Plaintiffs' expert Suzanne Parisian, M.D. (Doc. 1299).

"When faced with a proffer of expert scientific testimony, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" Polski, 538 F.3d at 838 (quoting Daubert, 509 U.S. at 592–93). Thus, under Rule 702, the trial judge also acts as a gatekeeper by screening evidence for relevance and reliability. Daubert, 509 U.S. at 589.

The district court applies a three-part test when screening expert testimony under Rule 702:

> First, evidence based on scientific, technical, or other specialized knowledge must be useful to the finder of fact in deciding the ultimate issue of fact. This is the basic rule of relevancy. Second, the proposed witness must be qualified to assist the finder of fact. Third, the proposed evidence must be reliable or trustworthy in an evidentiary sense, so that, if the finder of fact accepts it as true, it provides the assistance the finder of fact requires.

Polski, 538 F.3d at 839 (quoting Lauzon v. Senco Prods., Inc., 270 F.3d 681, 686 (8th Cir. 2001)).

"Rule 702 reflects an attempt to liberalize the rules governing the admission of expert testimony. The rule clearly is one of admissibility rather than exclusion." Lauzon, 270 F.3d at 686 (internal quotations and citations omitted). "The exclusion of an expert's opinion is proper only if it is so fundamentally unsupported that it can offer no assistance to the jury." Wood v. Minn. Mining & Mfg. Co., 112 F.3d 306, 309 (8th Cir. 1997) (internal quotations and citation omitted).

When assessing the reliability of expert testimony, a trial court should consider several factors, including: "(1) whether the concept has been tested, (2) whether the concept has been subject to peer review, (3) what the known rate of error is, and (4) whether the concept is generally accepted by the community." Miller v. Baker Implement Co., 439 F.3d 407, 412 (8th

Cir. 2006) (citing Daubert, 509 U.S. at 593–95). There is no requirement that courts rely on each factor, as the gatekeeping inquiry is flexible and must be "tied to the facts" of the particular case. Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (quoting Daubert, 509 U.S. at 591).

"[T]he rejection of expert testimony is the exception rather than the rule." Robinson v. GEICO General Ins. Co., 447 F.3d 1096, 1100 (8th Cir. 2006) (citing Fed. R. Evid. 702 advisory comm. note). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 595.

III. ARGUMENT AND ANALYSIS

Organon presents this Court with an "umbrella" motion seeking to exclude opinions by five of Plaintiffs' experts. Rather than addressing the qualifications of any particular expert in depth, Organon offers a few testimonial statements stripped of all context.

Organon appears to be operating under the assumption that a meticulous and particularized review of experts' opinions is unnecessary where each expert's opinion shares a critical flaw. Unfortunately, Organon has neglected to set forth the precise opinions that are now under attack. Instead, Organon asks that I exclude all testimony touching estrogen "bursts" or "variability." Organon's arguments are cursory at best and in many cases rely on the testimony of one expert to attribute a deficiency to the methods of the remaining experts.

A. Qualifications

1. Bursts or Variability of NuvaRing

Organon argues that I should exclude all testimony related to estrogen bursts or variability because none of Plaintiffs' experts are qualified in the field of pharmacokinetics.

However, as stated previously, I have already held that Dr. Tischkau is qualified as an expert in the field of pharmacokinetics. Organon's argument as to Dr. Tischkau is moot. Given the unparticularized nature of this motion, that should end the inquiry. However, in the interest of justice, and to avoid confusion, I will address the remaining challenged experts: Drs. Roseff, Parisian, Shumway, and Richart.

Dr. Scott Roseff is a board-certified doctor in obstetrics/gynecology as well as reproductive endocrinology and infertility. (Doc. 1381, Exh. 26, "Dr. Roseff C.V."). Although he does not hold himself out as an expert pharmacologist, he testified that he has background training in pharmacokinetics and has participated at least one pharmacokinetic study. (Doc. 1381, Exh. 27, "Dr. Roseff Depo.," at 117, 150). Dr. Roseff has authored or co-authored fourteen studies, including one which measured the disappearance of oestradiol and progesterone from pregnant women after delivery. (Dr. Roseff C.V.). I find Dr. Roseff qualified to testify about estrogen bursts and variability.

Organon relies upon out-of-context admissions by Plaintiffs' remaining experts that they are not pharmacokineticists. However, this does not necessarily foreclose their qualifications to testify as experts. See Doe v. Cutter Biological, Inc., 971 F.2d 375, 385 (9th Cir. 2002) ("Ordinarily, courts impose no requirement that an expert be a specialist in a given field, although there may be a requirement that he or she be of a certain profession, such as a doctor.") (citing McCormick, On Evidence, § 13, at 34 (3rd ed. 1984)); Holbrook v. Lykes Bros. S.S. Co., Inc., 80 F.3d 777, 782 (3d Cir. 1996) ("[I]t is an abuse of discretion to exclude testimony simply because the trial court does not deem the proposed expert to be the best qualified or because the proposed expert does not have the specialization that the court considers most appropriate.").

In any case, I am not persuaded that expertise in pharmacokinetics is itself a prerequisite to all testimony related to bursts or variability in NuvaRing's estrogen delivery.[5] Much of the testimony being challenged relates to the manner in which Organon displayed—or, allegedly, omitted—pharmacokinetic data in studies, reports, tables, and charts. Each of Plaintiffs' experts possesses sufficient knowledge, training, and experience to gauge the accuracy of that information. I have already found Dr. Parisian qualified to analyze and rely upon expert reports, including those based in pharmacology, when forming her own conclusions. [6] I likewise find Plaintiffs' remaining experts, Drs. Shumway and Richart, qualified to evaluate and rely upon pharmacokinetic studies and reports when reaching conclusions within their respective fields.[7] Organon's motion as to the qualifications of these experts regarding bursts and variability is denied.

2. Labeling

Organon next challenges the qualifications of Drs. Tischkau, Shumway, and Roseff to opine that the NuvaRing label itself should have provided additional information on variability. Organon argues that such testimony is foreclosed as none of the three possesses actual experience in the labeling of prescription drugs.

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[5] Organon's own internal documents refer to "burst effects" and "a large intra-individual variation in . . . EE for NuvaRing." See, e.g., (Doc. 1381, Exh. 7, "Expert Report on the Clinical Documentation of NuvaRing" at 12, 15).

[6] See Order dated March 4, 2013.

[7] Dr. Joseph Shumway is a physician board-certified in obstetrics/gynecology and has authored or co-authored nineteen peer-reviewed studies. (Doc. 1381, Exh. 30, "Dr. Shumway C.V."). Since 2002, Dr. Shumway has served on the editorial board of the *Journal of Reproductive Medicine*. Id. Dr. Shumway opines that the variability data was concealed and that, had he been aware of the estrogen variability, he would not have prescribed NuvaRing to his patients. (Doc. 1381, Exh. 31, "Dr. Shumway Report," at 8). Dr. John Richart is an associate professor of medicine and a board-certified hematologist. (Doc. 1381, Exh. 34). He has authored or co-authored at least nine peer-reviewed studies. Id.

Drs. Shumway and Roseff are practicing OB/GYNs who make prescription decisions on a regular basis. Accordingly, these experts are qualified to opine as to how knowledge obtained through studies, reports, Organon documents, and the NuvaRing label itself would have affected and did affect their prescription-related decisions. I further agree with Judge Herndon that "doctors are 'fully qualified to opine on the medical facts and science regarding the risks and benefits of [drugs] . . . and to compare that knowledge with what was provided in the text of labeling and warnings for FDA approved drugs.'" In re Yasmin & YAZ (Drospirenone) Mktg., Sales Practices & Products Liab. Litig., 3:09-MD-02100-DRH, 2011 WL 6301625 (S.D. Ill. Dec. 16, 2011) (alterations in original) (quoting In re Diet Drugs Prods. Liab. Litig., MDL 1203, 2000 WL 876900, * 11 (E.D. Pa. June 20, 2000)). I likewise find that Dr. Tischkau, as a physiologist, assistant professor in pharmacology, and academic reviewer for numerous publications, possesses the qualifications to compare existing data and knowledge with what was provided in the text of NuvaRing's label and warnings. Organon's motion regarding the qualifications of these experts to testify about labeling is denied.

B. Reliability

1. Testimony that Variability in Estrogen is Significant or Dangerous

Organon argues that I should exclude opinions that the variability in estrogen levels of women using NuvaRing presents an increased risk of adverse effects, including VTE. However, I have already ruled on a related motion that Plaintiffs may present expert testimony on a theory of "progestin counterbalancing."[8] In short, Plaintiffs' experts opine that the progestin component of hormonal contraceptives counterbalances the prothrombotic effects of the estrogen component. They further opine that the bursts or variability in estrogen levels are unaccompanied by corresponding increases in progestin and, therefore, the bursts and variability

[8] See Order dated March 4, 2013.

present an increased risk of adverse hematological events. Insofar as Organon is attempting to relitigate that issue, I will deny Organon's motion as moot.

2. Testimony about the Relationship between Estrogen Serum Concentrations and NuvaRing's Hormone Release Rate

Organon next argues that variations in the amount of hormones measured in blood serum cannot show that NuvaRing's rate of release differs from the rate reflected in its label. Organon alleges that Plaintiffs' experts have no scientific support to show that blood serum concentrations relate to hormone release rates. Organon also argues that Plaintiffs' experts cherry picked favorable data in support of their opinion.

Contrary to Organon's arguments, I find that there exists support within the scientific literature that blood serum levels may be used to show rate of hormone release. Organon's own reports found that a linear correlation could be established between the in-vitro release rate and the in-vivo release rate, based on blood serum data taken during the pharmacokinetic clinical trial No. 34218. (Doc. 1381, Exh. 7, "Expert Report on the Clinical Documentation of NuvaRing," Dec. 2006, at 22); see also Doc. 1381, Exh. 6, NuvaRing Report Dec. 8, 1999, at pt. 4.2.1 (noting Clinical Trial No. 34218 established quantitative correlation between in-vitro release rate and in-vivo absorption rate)).

Dr. Roseff opines that the varying levels of EE in clinical patients' blood serum indicates that NuvaRing's release of EE fluctuated. (Doc. 1381, Exh. 25, "Roseff Report" at 20). I find that Dr. Roseff's opinion is based on reliable methodology. Although Organon may disagree with Dr. Roseff's conclusions, such disputes must be reconciled by the jury.

Allegations that Plaintiffs' experts "cherry picked," or cited only to data that supported their opinion and ignored unfavorable data, must wait until cross-examination. See Kuhn v. Wyeth, Inc., 686 F.3d 618, 633 (8th Cir. 2012). Organon may choose to present its experts'

contrary conclusions at trial. As a result, I will deny Organon's motion to exclude testimony related to the relationship between blood serum concentrations and hormone release rate.

3. Testimony that the NuvaRing Label Did Not Disclose Variability Data

Organon next argues that I should bar testimony that the NuvaRing label is inadequate for failure to include information regarding variability of serum concentrations or other pharmacokinetic parameters. Organon bases this argument on two premises: first, that the label does include some variability data, and second, that Plaintiffs fail to show how the label could more completely disclose variability.

Organon's first argument, that the label includes some variability data, does not preclude the challenge by Plaintiffs' experts to the label. This argument merely reflects a conclusion that differs from the one presented by Plaintiffs' experts and must, therefore, wait until trial.

Organon next argues that none of Plaintiffs' experts have drafted an alternative NuvaRing label and, therefore, their opinions that the label is inadequate should be considered unreliable as a matter of law. The cases cited by Organon are factually dissimilar to this MDL.

In Jarequi, the appellate court affirmed the exclusion of experts who testified that manufacturer warnings on a mobile farming combine were insufficient. Jarequi v. Carter Mfg. Co., 173 F.3d 1076, 1084–85 (8th Cir. 1999). In that case, the manufacturer's warnings had twice been painted over by persons other than the manufacturer; the plaintiff had also admitted to using the combine improperly despite numerous warnings by individuals, including warnings immediately prior to his injury. Id. at 1084. The plaintiff's experts testified that the warnings should have been bigger, closer to the point of danger, and should have used chevrons to dissuade owners from painting over the warnings. Id. at 1080. The court held this testimony to be unreliable because the experts had not read the existing warnings, had not created their

proposed warnings, and could not state that their proposed warnings would not also have been painted over. Id. at 1084.

In Milanowicz v. Raymond Corp., the expert provided no analysis as to how a different warning would prevent the plaintiff's injury by a mechanical fork lift, did not create an alternative warning, and could cite no evidence that a change in warning would convey more appropriate information to future users of the device. 148 F. Supp. 2d 525, 541 (D. N.J. 2001). Likewise, in *Kilgore*, the expert opined that an audible warning would effectively notify an escalator's owner when the escalator stopped and that these warnings were "industry standard." Kilgore v. Carson Pirie Holdings, Inc., 205 Fed. App'x. 367, 372 (6th Cir. 2006). However, the Kilgore expert could cite no evidence that such a warning was actually the standard; there were no independent requirements for such a warning; and the expert conducted no research as to whether such a warning would work as hypothesized. Id.

In contrast to the factual circumstances underlying Organon's cited cases, Plaintiffs' experts articulate specific deficiencies in the NuvaRing label and accompanying documents that they believe affected prescribing decisions. For example, Dr. Roseff states that the NuvaRing label's representation that there is no significant variability in the delivered dose of EE is inaccurate, given the variable levels of EE in patient blood serum found in Clinical Trial No. 34218. (Doc. 1381, Exh. 25 at 6). Additionally, Dr. Tischkau asserts that Figure 1 on the NuvaRing label improperly excludes several data points of serum EE, which results in an inaccurate depiction of NuvaRing's pharmacokinetic profile. (Doc. 1381, Exh. 3 at 12–13). Dr. Tischkau further opines that the stated n-value of 16 in Figure 1 should be lower to reflect that several subjects' data were excluded. Id.

I find that Plaintiffs have carried their burden of demonstrating the reliability of testimony that NuvaRing's label contains inaccuracies related to pharmacokinetic parameters. As a result, Organon's argument that I should exclude testimony by Plaintiffs' experts regarding this challenge to the label is denied.

4. Relevance of Variability in Estrogen Delivery

Organon next alleges that I should prohibit testimony related to variability in estrogen delivery because such testimony is irrelevant and therefore cannot assist the trier of fact to understand the evidence.

Contrary to Organon's arguments, I find that testimony about variability will assist the trier of fact. Plaintiffs' claims are based in part upon strict liability. I have already ruled that Plaintiffs may produce testimony that NuvaRing presents a greater risk for VTE than represented by Organon. Plaintiffs' experts intend to testify that the variable nature of NuvaRing's estrogen delivery results in periods during which the progestin component cannot counterbalance estrogen's prothrombotic effects. Testimony about variability in estrogen delivery will be of assistance to the jury in determining the merits of this claim.

Moreover, even were it necessary to produce evidence that variability directly caused each Plaintiff's injury, such an inquiry would necessitate a case-by-case examination of the evidence. I cannot at this stage foreclose the admission of testimony related to variability. Organon's argument that such testimony will be unhelpful to the jury is denied.

5. Relevance of a Different Pharmacokinetic Warning

In its final point, Organon alleges that no evidence has been provided to show that any physician would have changed a NuvaRing prescribing decision if the NuvaRing label had incorporated a pharmacokinetic warning or if the pharmacokinetic data had been presented

differently. However, Dr. Shumway stated that had he been aware of the estrogen variability, he would not have prescribed NuvaRing to his patients. (Doc. 1381, Exh. 31, "Dr. Shumway Report," at 8). In any case, Organon's request requires a particularized evaluation of the facts on a case-by-case basis. This inquiry is inappropriate at this time. Organon's argument as to the relevance of different pharmacokinetic labeling is denied.

IV. CONCLUSION

For the foregoing reasons, I find Plaintiffs' experts are qualified to opine as to the matters challenged. Further, these opinions, as grounded in credible articles, studies, reports, and personal experience, are based on a reliable methodology. The opinions challenged herein will also provide assistance to the finder of fact.

Accordingly,

IT IS HEREBY ORDERED that Organon's motion to exclude testimony related to "bursts" or "high variability" in NuvaRing's estrogen delivery [Doc. 1309] is **DENIED.**

RODNEY W. SIPPEL
UNITED STATES DISTRICT JUDGE

Dated this 5th day of March, 2013.